EXHIBIT 2

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC., **PELVIC REPAIR SYSTEM PRODUCTS** **LIABILITY LITIGATION**	**Master File No. 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**
THIS DOCUMENT RELATES TO **WAVE 2 CASES**	

GENERAL EXPERT REPORT OF MICHAEL KARRAM MD FACOG FPMRS

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General Expert Report of Michael Karram MD FACOG FPMRS

I am a sub-specialist in the field of Female Pelvic Medicine and Reproductive Surgery. I am double boarded in Obstetrics and Gynecology (1986) and Female Pelvic Medicine and Reconstructive Surgery (2014). I am licensed to practice medicine in Ohio, Kentucky and Indiana. I am currently the Division Director of FPMRS at Seven Hills Women's Health Centers a large multi-specialty group. I also am the Director of the Minimally Invasive Gynecologic Fellowship at The Christ Hospital in Cincinnati, Ohio. I serve as the Medical Director of the Pelvic Floor Center at Mercy West Hospital in Cincinnati, Ohio. I hold an academic title of Associate Professor in the department of Obstetrics and Gynecology University of Cincinnati, College of Medicine.

After graduating from medical school, I completed my residency in Obstetrics and Gynecology at Good Samaritan Hospital Cincinnati, Ohio. This was a large private hospital doing over 6,000 deliveries per year and a large volume of gynecologic surgery. After graduating residency I went into private practice in Obstetrics and Gynecology. I took care of a wide variety of conditions including advanced pelvic organ prolapse and genito-urinary complications of vaginal and cesarean birth.

In 2010 I gave up obstetrics and focused on gynecology. My area of expertise is advanced pelvic surgery, minimally invasive surgery, pelvic organ prolapse, and bladder conditions including incontinence and voiding abnormalities. In my career I have utilized all

forms of surgery in the treatment of these conditions. This would include abdominal, vaginal, laparoscopic, and robotic procedures. These were native tissue repairs, augmented repairs with biologics, augmented repairs with synthetic mesh and suture augmented repairs.

A chronology of my education, training and experience is outlined below:

1973:	BS Ohio State University Columbus, Ohio
1978:	MD Cairo University Faculty of Medicine (Honors) Cairo Egypt
1979-80:	Internship Case Western Reserve Cleveland Ohio
1980-84:	Residency Good Samaritan Hospital Cincinnati, Ohio
1983:	Two week clerkship in Urogynecology with Dr. Donald Ostergard Long Beach Memorial Hospital
1984-2001:	Obstetrics and Gynecology Private Practice Cincinnati, Ohio
2001-Pres:	Gynecology Practice focusing on gynecologic surgery and Urogynecology
1986:	Board Certification, American College of Obstetrics and Gynecology
1986:	Diplomate, American Board of Obstetrics and Gynecology
2014:	Board Certification, Female Pelvic Medicine and Reproductive Surgery
1998-Pres:	Director, Urogynecology Seven Hills Women's Health Centers Cincinnati, Ohio
2013-Pres:	Director, Fellowship Minimally Invasive Gynecologic Surgery, Christ Hospital Cincinnati, Ohio
2015-Pres:	Medical Director Pelvic Floor Center Mercy West Hospital Cincinnati, Ohio
1998-2013:	Consultant, Proctor, Preceptor and Trainer for Ethicon/Gynecare
2000-Pres:	Consultant, Proctor, Preceptor and Trainer for American Medical Systems (Astora)
2013:	Presenter at AUGS meeting
2015:	Presenter at AUGS meeting

I am a member of the following organizations:

Member American Urogynecoloic Society (AUGS)
Member International Urogynecologic Association (IUGA)
Member American Association of Gynecologic Laparoscopists (AAGL)

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In my experience, I have utilized many surgical procedures. This would include vaginal, abdominal, laparoscopic and robotic hysterectomy. Native tissue repairs for cystocele, rectocele, and enterocele. Sacrocolpopexy, utero-sacral ligament suspension, sacrospinous fixation, ilieococcygeus suspension, and McCalls culdoplasty for vaginal vault prolapse. Obliterative procedures Le-Fort or colpocleisis. Marshall Marchetti Krantz, Burch, paravaginal repairs, Perrerya, Stamey, pubo-vaginal facial slings, TVT, TVT-O, TVT-Abrevo, TVT-secur, monarc, top down retropubic procedures for stress urinary incontinence.

I have a very extensive experience with surgical procedures that utilize mesh. I have performed over 2,000 synthetic sling procedures using both mechanical and laser cut mesh. I have used Gynemesh PS for anterior repair augmentation as well as abdominal sacrocolpopexy. I have used many vaginal mesh kits including anterior and posterior Prolift, apogee and perigee, and anterior and posterior Elevate. I have performed over 500 mesh kit repairs in the treatment of POP.

I am nationally and internationally known in the field of gynecologic surgery and advanced pelvic surgery. As an expert at treating both stress incontinence and pelvic organ prolapse, I have extensive experience using native tissue and augmented repairs. I have been performing TVT since 1998 and have experience with retropubic, transobtrurator, and single incision slings. I have also performed a large number of mesh augmented pelvic organ prolapse surgeries.

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I am a reviewer for the Journal of Obstetrics and Gynecology. I hold leadership positions in the hospitals I am affiliated with, as well as the American Urogynecologic Society.

As a consultant for the above listed companies I participated as lead faculty at many sling courses and mesh augmented prolapse courses. These courses would include a didactic portion and a cadaver training portion. A lengthy discussion on indications, techniques, complications, management of complications and consenting patients correctly would follow each session. Upon completing these course participants were well versed in:

- Patient selection
- Correct consent process
- Understanding the IFU of the product/products
- Surgical technique
- Implant the procedure completely on the cadaver
- Understand possible complications and how to manage them
- When to refer complicated or difficult patients

My hourly rate for review of materials is $500.00 per hour. In the last four years I've testified in the following cases:

Sharon Boggs et al. v. Ethicon, Inc., et al.; In The United States District Court For The Southern District Of West Virginia Charleston Division; Case No. 2:12-cv-00368

Donna Massey et al. v. Ethicon Inc. et al.; In The United States District Court For The Southern District Of West Virginia Charleston Division; Case No. 2:12-cv-00880

Paula Kriz et al v. Ethicon, Inc. et al.; In The United States District Court For The Southern District Of West Virginia Charleston Division; Case No. 2:12-cv-00938

Margaret Kirkpatrick v. Ethicon, Inc., et al.; In The United States District Court For The Southern District Of West Virginia Charleston Division; Case No. 2:12-cv-00746

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Miranda Patterson v. Ethicon, Inc., et al.;In The United States District Court For The Southern District Of West Virginia Charleston Division; Case No. 2:12-0481

Thelma Wright v. Ethicon, Inc. et al. .;In The United States District Court For The Southern District Of West Virginia Charleston Division; Case No. 2:12-cv-1090

Opinions:

All my opinions are held to a reasonable degree of medical and scientific certainty and probability. All my opinions are based on my education, training, clinical experience, medical literature and materials I have reviewed, my discussion with colleagues, my research, and feedback from my patients. I also draw opinions from meetings I have attended including but not limited to AUGS, ACOG, SUFU, SGS, AUA, IUGA and other professionally sponsored programs. I reserve the right to amend or modify my opinions in this case as additional facts are received.

History:

The demand for treatment of pelvic floor disorders, such as pelvic organ prolapse (POP), is estimated to increase by 45% by 2030 (Luber 2001) and the lifetime risk of a woman undergoing prolapse surgery is 13% (Wu 2014). In the United States, more than 300,000 prolapse surgeries are performed each year (Shah 2008). Among these women, recurrence rates associated with traditional native tissue repairs as high as 58% have been reported, and 205-30% will undergo reoperation (Whiteside 2004, Denman 2008).

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Pelvic organ prolapse is described as a condition where the pelvic organs, uterus, bladder, bowel, and vagina protrude abnormally into or beyond the vaginal opening causing symptoms. This is attributed to the weakness in the support structures that normally support these organs. This is usually caused by stretching, tearing, and weakening of these tissues. There are a variety of reasons this can occur. Childbirth, congenital or acquired connective tissue abnormalities, trauma, denervation, menopause, aging, hysterectomy, smoking, chronic cough, and conditions of increased abdominal pressure are all related to a higher risk of POP (Bump 1998, Gill 1998, MacLennan 2000).

The common conditions seen are uterine prolapse, cystocele, rectocele, enterocele, perineocele, vault prolapse, and stress urinary incontinence. This leads to symptoms of vaginal bulge, pressure, and the feeling that something is protruding from their vagina. Sometimes it comes out and goes back in, other times it stays out consistently or has to be manually replaced. This causes a variety of complaints such as urine leakage, recurrent urinary tract infection, inability to empty the bladder completely, the need to digitally manipulate the bladder to empty, or sit in certain positions to empty. The same can occur with the bowel, incontinence, constipation, digital manipulation, squatting or splinting to have bowel movements. It can also cause pelvic pain, dyspareunia, vagina bleeding, chronic vaginal sores, low back pain, constipation, and chronic vaginal discharge (Johnson 2013). This leads to cleanliness issues especially in the elderly population with limited mobility.

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Women with POP suffer in silence for long periods of time. Many women feel this is a natural aging process, there is nothing that can be done, or if something is done it will fail as it did with family members and friends. It affects their social, physical, and psychologic wellbeing (Abdel-Fattah 2011). Sexual dysfunction is not only due to pain or discomfort from the prolapse, but also to a negative body image and embarrassment about the condition (Barber 2002). Women seeking treatment for POP have decreased body image and quality of life (Handa 2008). Some conditions such as OAB when a cystocele is present maybe independent of the POP itself (Maher 2013).

Treatment:

There are many options in the treatment of pelvic organ prolapse. Many women choose to do nothing. It is a quality of life issue, and women state that it is not affecting their lifestyle, they choose to observe. Once the realization that this is not a potentially fatal condition, some woman learn to live and deal with their condition.

A **pessary** is a non-surgical approach to manage POP.

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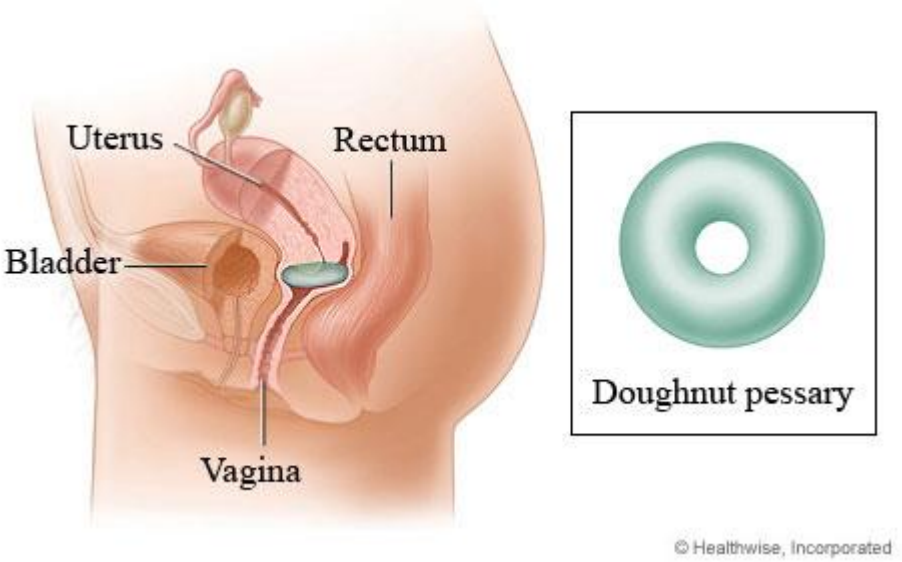

The pessary comes in different sizes and shapes. It is designed to hold the pelvic organs that have prolapsed in a normal anatomic position. It is placed in the upper vagina between the symphysis pubis and the sacrum. Success rates of up to 62% have been reported in stage III and stage IV POP. (Jones 2010).

Obliterative procedures such as the Le-Fort and colpocleisis are viable options for the non-sexually active female.

Surgical procedures are designed to address the level of support that has been lost. Pelvic support is labeled as level I, II, or III.

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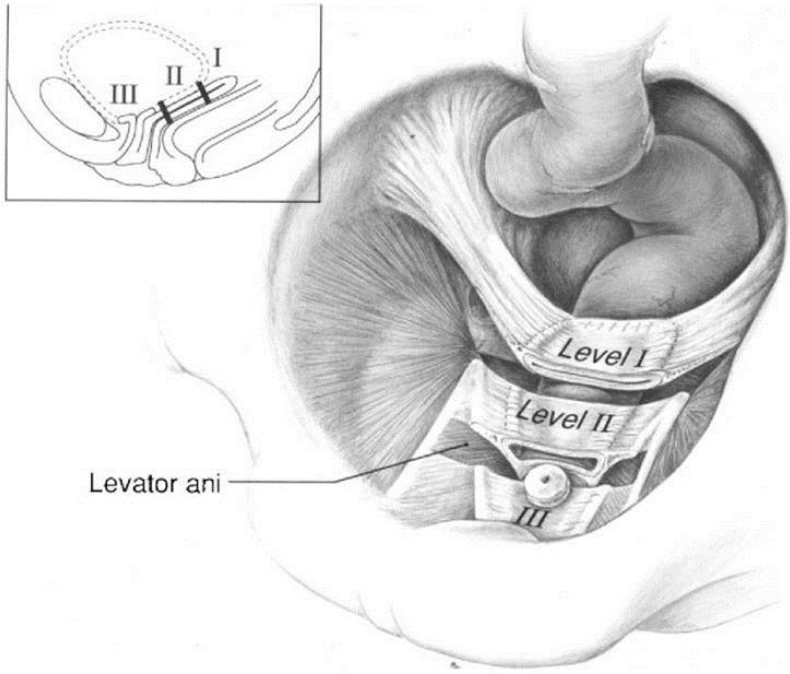
De Lancey's Levels

I. Uterosacral cardinal ligament

II. ATFP

III. Perineal membrane and perineal body



Level I support is apical support and coincides with the ligamentous support provided by the utero-sacral and cardinal ligaments. Level II is paravaginal support and Level III is perineal support. Level I or apical procedures would include ASC, sacrospinous fixation, utero-sacral ligament suspensions, ilieococcygeous suspensions and mesh kit repairs that had an attachment to the sacrospinous ligament. Level II procedures would be anterior colporraphy and paravaginal repairs. Level III procedures would include colpoperinorraphy.

Cystocele is the most common type of prolapse (Hendrix 2002). In a 10 year retrospective cohort study of 142 women, cystocele was the most common primary prolapse (87%) and recurrent prolapse (72%)(Fialkow 2008).

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Native tissue repairs, historically, have had a high recurrence rate in the anterior compartment. Rates of 30% - 60% have been reported (Maher 2011, Jia 2010). Jia performed a systematic review of safety and efficacy of mesh augmented anterior repair and traditional native tissue repair and found mesh repair significantly reduced recurrence (76.9% to 71.2% respectively).

Because of the lack of standardization in the performance of native tissue repair, historically, it was very difficult to compare data on results. Weber and colleges conducted a three arm RCT looking at standard anterior repair, standard plus mesh, and ultralateral anterior repair. Failure to have satisfactory or optimal anatomic response was reported in 70%, 58%, and 54% respectively (Weber 2001). Other reports showing high reoperation rates included 30% (Olsen 1997) and 43%-58% (Clark 2003) (Whiteside 2004). It was widely referred to, when speaking to patients about procedures and failure rates, that a range from 30%-50% is quoted frequently. Failure rates have been shown to be extremely high for native tissue repairs (Benson 1996, Lovatis 2003, Hardiman 1996, Whiteside 2004, and Aultman 2011).

Level II support procedures are designed to give hammock support to the vagina from ATFP to ATFP. Most traditional cystocele repairs attempt to create this Level II support by placating the pubo-cervical septum or by performing a paravaginal repair. Level III support procedures support the perineal membrane and body.

Use of mesh in pelvic floor surgery has been in existence since the 1960s. Due to the failure/recurrence rate, surgeons have used augmented repairs to increase the longevity or the

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repair. Multiple studies have demonstrated a statistically significant difference in a mesh augmented procedure vs a traditional repair 33% vs 16% (Benson 1996), 43% vs 25% (Sand 2001), and 38.5% vs 6.7% (Hiltimun 2007).

All POP surgeries have many risks associated with them. This can include infection, hemorrhage, urinary tract injury, bowel injury, voiding dysfunction, bowel dysfunction, pelvic pain, dyspareunia, sexual dysfunction, suture erosion (permanent suture), granulation tissue, vaginal canal shortening/narrowing, failure and recurrence (Sokol 2012, Toglia 2008, Yazdany 2010, Svabik 2014, Barber 2014, Diwadkar 2009, Dietz 2013). This is also elicited in the ACOG Committee Opinion 2011 and the AUA 2011 Position Statement on the use of vaginal mesh in POP.

Any surgeon who performs pelvic floor surgery has as his/hers training, medical school, residency, +/- fellowship, work with skilled surgeons in their field of expertise, society and college meetings and CME courses set up by societies to increase the knowledge base of the surgeons. Within this long educational process, surgeons become aware of all the above risks related to pelvic floor surgery. There is no need for a manufacturer or any other non-educational entity to inform surgeons of these risks. They are adequately trained to understand and manage them.

Gynemesh PS was approved in 2002 by the FDA for use in pelvic reconstructive surgery. As a thread it is widely used as a durable permanent surgical suture. As a knitted material, polypropylene mesh is used as a graft material in many parts of the human body, most notably,

in the abdominal wall for hernia repairs. In the field of female pelvic surgery Type I, macroporous, monofilament, light weight mesh is used most frequently. It has been demonstrated to be safe and effective (Nilsson 2013, AUGS SUFU Position Statements on Mesh MUS for SUI 2014). Macroporous mesh is well suited for vaginal surgery as it allows fibroblasts, macrophages, blood vessels and collagen entry into the mesh thus minimizing infection. In the Ford Cochrane review 2015, Type I polypropylene mesh is recognized as the highest biocompatibility with the lowest risk of infection. I have been using mesh in my practice for approximately 20 years, and my experience concurs with the above findings. This would include abdominal sacrocolpopexy, free cut mesh to augment repairs, TVT, and various vaginal mesh kits for the management of POP.

Due to the efficacy and safety profile of Gynemesh PS (Julian 1996, Migliari 2000, Berrocal 2004, and Lucente 2004), the prolift system was developed. The premise was to take a safe effective mesh, that has proven success, and piggyback on the success and efficacy of TVT, to develop a minimally invasive procedure that is standardized, safe, effective, and addresses the issues of recurrence and failure of traditional procedures.

Multiple surgeon groups and iterations were evaluated until the final Prolift system was developed. It was a transobturator approach with two arms, one at the level of the bladder neck and the second down to the ischial spine. The second portion was a transgluteal pass through the ishio-rectal fossa and the sacrospinous ligament (SSL).

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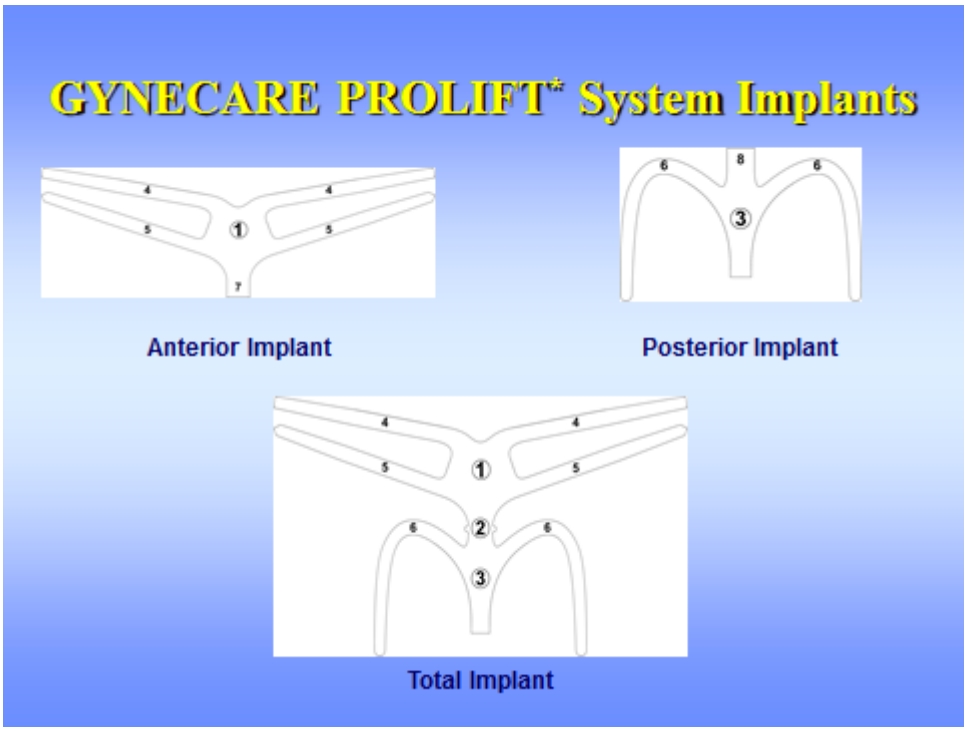

The system was designed to give lateral support from ATFP to ATFP, therefore restoring Level II support. Its posterior arm attached to the SSL, therefore restoring Level I support. The mesh was delivered via a cannula retrieval system that was safe, effective, and was always under direct palpation of the surgeon's fingers and hands.

The anterior mesh is placed in the vesico-vaginal space and the posterior mesh in the recto-vaginal space. These are two spaces are easy to identify and are the exact same space that the mesh used in sacrocolpopexies is placed. It mirrors the location vaginally that is used abdominally.

There have been several RCTs comparing Gynemesh PS and Prolift to native tissue repairs. They establish efficacy, safety, and anatomic results as well as subjective and QOL

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improvements. The prolift procedure has been studied in over 100 studies, more than any other surgical device used in the treatment of POP. There are many RCT showing a better anatomic and subjective result with Prolift vs traditional repair. Based on my extensive review of the medical literate coupled with my own vast clinical experience, I believe that Prolift was a safe and efficacious procedure to treat POP.

Study	# Patients	Compartment	Mesh Anatomic Cure	Native Anatomic Cure	P value
Carey 2009*	139	Ant & Post	81%	65.6%	P=.07
Withagen 2011	194	All	90%	55%	p<.001
Altman 2011	389	Anterior	82%	48%	p=0.008
Sokol 2012	65	All	38%	30%	P=0.445
Halaska 2012	168	All	83.1%	60.6%	P=0.003
El Nazer 2012*	44	Anterior	80%	35%	P<0.05
Qatawneh 2013*	116	All	79%	62%	P=0.043
Svabik 2014	70	All	97%	35%	P<0.001
DaSilveira 2014	184	Anterior	86.4%	70.4%	p=0.019

*Gynemesh PS

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Table 5 Results of Prolift surgery according to the previous literature

Series (reference)	No. patients	Device	Type	Mean follow up	Cure rate (anatomical)	Mesh exposure	Study design
Present series	75	Prolift	Anterior: 51 Posterior: 3 Total: 20	54 months	81.5%	5.3%	Retrospective
de Landsheere 2011[14]	526	Prolift	Anterior: 48 Posterior: 103 Total: 373	38 months†	N/A	3.6%	Retrospective
Vaiyapuri 2011[16]	254	Prolift	Anterior: 106 Posterior: 20 Total: 128	12 months	95.6%	11.5%	Retrospective
Milani 2011[17]	127	Prolift+M	Anterior: 41 Posterior: 16 Total: 70	12 months	77.4%	10.2%	Prospective
Huang 2011[13]	65	Prolift	Total: 65	24.5 months†	94%	2%	Retrospective
Wetta 2009[18]	50	Prolift	Anterior: 16 Posterior: 16 Total: 18	14 months	98%	2%	Prospective
Van Raalte 2010[19]	91	Prolift	Anterior: 46 Posterior: 28 Total: 23	19 months†	86.6%	0%	Prospective
Nair 2011[20]	60	Prolift	Anterior: 21 Posterior: 12 Total: 27	29 months	85%	15%	Prospective
Elmer 2009[21]	252	Prolift	Anterior: 121 Posterior: 68 Total: 63	12 months	80%	11%	Prospective
Hollander 2010[23]	323	Prolift	Anterior: 88 Posterior: 91 Total: 144	20 months	87%	11.5%	Retrospective

†Median follow up.

According to the latest Cochrane review (Maher 2013) of 5,954 women, traditional repair was associated with a higher anterior compartment recurrence on exam than any of the mesh repairs (CI 2.50-3.96). Altman reported on 389 women in a RCT, 200 Prolift and 189 traditional. Women who underwent an anterior Prolift had a lower failure rate (39.2%) vs traditional repair (65.5%) p<.001. Pain and sexual function showed no difference between the groups and there was a 3% mesh revision rate. There was no statistically significant difference

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in de novo dyspareunia, genital pain, vaginal length, or sexual function based on the PISQ-12 questionnaire.

Surgical intervention for mesh exposure was 3.2% in the Aultman study. This is consistent with other studies. De Landsheere 2012 reported on 524 Prolift patients with a mesh exposure rate requiring surgical intervention of 2.5%. Benbouzoid 2012 reported on 75 patients with a follow-up of 54 months, with a mesh exposure rate of 5.3%. Two required excision and two were treated with estrogen cream. At last follow-up 85% were cured with no prolapse recurrence.

Recently, Nygaard and colleagues published the long term result of the CARE study which was a NIH funded study. CARE (Colpopexy and Urinary Reduction Efforts) was a study comparing ASC without Burch to ASC with Burch. Study was stopped early because the numbers of women without Burch were developing urinary incontinence more frequently the Burch group. This reached statistical significance and the study was stopped. Conclusions were to offer an anti-incontinence procedure to patients undergoing ASC. At 7 year follow-up 126 women were available for long term follow-up. Probability of mesh erosion was 10.5%. An updated composite endpoint of failure using anatomic and subjective measures was 48% for ASC and B vs 34% for ASC no B. 5% of the study population had undergone surgical retreatment for prolapse recurrence.

Meyer 2016 has reported on the longest follow-up of transvaginal mesh patients in the literature. 70 patients of 208 completed questionnaires and 48 were available for both

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postoperative examination and questionnaire. Mean follow-up was 7 years (5.8-8.1 years). POP-Q measurements and overall pelvic organ prolapse stage were significantly improved ($p<.001$). Their conclusions were, women undergoing transvaginal mesh prolapse surgery using synthetic graft continue to have positive objective and subjective outcomes, leading to significantly improved QOL at 5 year follow-up.

Many RCTs comparing Prolift to SSL fixation procedures have shown many benefits to the Prolift procedure. These include more durable and less bleeding complications (Halaska 2012, Svabik 2014). Jacquetin 2013 did a prospective 5yr follow-up study on the use of transvaginal mesh in the treatment of POP.

Table 1 Randomised controlled trials comparing polypropylene mesh with traditional native vaginal tissue repairs

Reference	Total number patients	Follow up (months)	Compartment studied	Anatomic cure mesh (%)	Anatomic cure traditional (%)	*p*
Hiltunen et al. [9]	104	12	Anterior	93	62	<0.04
Sivaslioglu et al. [10]	90	12	Anterior	91	72	<0.05
Nieminen et al. [11]	105	24	Anterior	89	59	<0.05
Nguyen and Burchette [12]	75	12	Anterior	87	55	<0.05
Carey et al. [13]	139	12	Anterior Posterior	81	65.6	0.07
Nieminen et al. [14]	202	36	Anterior	87	59	<0.0001
Withagen et al. [15]	194	12	All	90	55	<0.001
Altman et al. [16]	389	12	Anterior	82	48	0.008
Sokol et al. [17]	65	12	All	38	30	0.45

Since 2005 there are more than 200 studies on Prolift. These were independent and sponsored studies. They have been presented in scientific peer review journals, at society meetings, and do experts in the field of pelvic surgery. Overwhelmingly, they consistent show the success of Prolift at achieving long-lasting anatomic cure with a low rate of complications.

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No other procedure has been studied as extensively as this procedure in the area of pelvic surgery to repair prolapse.

Medical societies (ACOG, AUGS, SUFU, AUA, SGS) have all put for favorable position statements in regards to mesh use in pelvic organ prolapse. Since these statements additional studies have been published showing Prolift is and effective and safe procedure in the treatment of primary and recurrent prolapse (Benbouzoid 2012, Landsheere 2012, Miller 2011, Jacquetin 2013)

When comparing Prolift to traditional repairs for POP, it becomes obvious that all pelvic floor surgeries have risks. All surgeries have risk of infection, hemorrhage, bowel injury, urinary tract injury, wound infection, hernias, dehiscence, vaginal scarring, pelvic pain, dyspareunia, failure, recurrence, voiding problems, defecation problems, DVT, PE, osteomyelitis, back pain and the need for repeat procedures to correct these issues if they do occur (Nygarrd 2013,Abed 2011, Toglia 2011, Yazdany 2010). In the recent Optimal trial USLVS vs SSLF, at 2 years success was 64.5% and 63% respectively, while suture exposure at 6 months to 2 years was 15.4% and 17.2 %. Vaginal granulation in the same time period was 19.1% and 14% respectively.

In the most recent Cohrane Review (Maher 2016) looking at native tissue repair vs transvaginal mesh these conclusions were reached:

- Awareness of the prolapse at 1-3 yrs was less likely in the mesh group (CI 0.54-0.81)
- The need for repeat surgery was less in the mesh group (CI 0.31-0.88)
- There was no difference in the need for another surgery for incontinence (CI 0.62-1.83)
- The incidence of surgery for mesh exposure was 8%

- Objective recurrent prolapse was less in the mesh group (CI 0.30-0.53)
- No difference in the occurrence of de-novo dyspareunia (CI 0.58-1.47)

Mesh Exposure:

An overall mesh exposure rate of 3%-8% is an acceptable rate by today's standards. The majority of these can be managed conservatively with estrogen cream or an in office resection under local anesthesia. In the rare instance a patient has to be taken back to the operating room for a resection under general anesthesia. These same issues occur with traditional native repairs and require similar management. In a RCT conducted by Iglesia and Sokol (2011), there was a 15% Prolift mesh exposure rate compared to a 15% rate of suture erosion in the native tissue repair group. Three facts should be noted about the study:

- The 15% exposure rate was a preset rate and the study was stopped
- Many of the exposures were asymptomatic or managed in the office with no future issues
- The insertion of the Prolift device was modified and not inserted based on the IFU or Ethicon/Gynecare recommendations. The deep arm of the anterior prolift was placed through the sacrospinous ligament instead of above the ischial spine as suggested in the IFU.

Company Training:

Ethicon/Gynecare did an excellent job of educating surgeons on the use of their products. As mentioned above in this document, I served as lead faculty on many training sessions. Thus, I

have an intimate understanding of what the reasonably prudent pelvic floor surgeon should know about the risks and benefits of pelvic floor procedures, the adequacy of the warnings in IFUs, the management of mesh complications, and the well-known risks that are associated with any pelvic floor surgery. It is common knowledge to pelvic floor surgeons that any surgery for stress urinary incontinence or pelvic organ prolapse, with or without the use of mesh, can potentially cause complications that can be temporary or permanent, including but not limited to: pelvic pain, dyspareunia (pain with sexual intercourse), scarring, vaginal narrowing, leg/groin pain, urinary retention and other voiding problems.

Ethicon's professional education process would begin with the representatives in the field surveying qualified surgeons that might be interested in the use of these devices. A qualified surgeon would be a urogynecologist or gynecologist who is experienced and knowledgeable in the surgical management of SUI. Hence, that is a major portion of their practice. They would be given information on the products, the IFUs, and clinical data to review before their training session. The training session would be two days and on Friday night there would be an in depth discussion between faculty and participants' about indications, contraindications, technique, complications and management of the complications. Saturday would be a full day in the cadaver lab 7am-5pm. A didactic presentation followed by a cadaver lab where every participant, under the supervision of the faculty member, would implant the device over and over again until the faculty member and participant were satisfied with the objectives.

The participants would receive a certificate verifying their attendance at the course. Faculty members would then meet with the Ethicon/Gynecare representatives and give them an evaluation of all the participants, specifically those that were felt to be deficient or weak in their technique or knowledge. Upon departure all participants were given our contact info to call if they had any questions or problems. They were also offered a preceptor to come to their institution and observe with their first few cases if they desired.

To facilitate these training sessions, Ethicon incorporated professional education slide decks into their Prolift slide decks). These slide decks not only provided technical guidance on how to perform a Prolift procedure, but they also provided pelvic floor surgeons with an

overview of success and complication rates of these devices as reported by the medical literature at the time. I have not only reviewed these slide decks, but I have taught other doctors from these decks at past professional education events sponsored by Ethicon.

Surgeon Credentialing:

Credentialing is done by the hospital credentialing committee, not by Ethicon/Gynecare. Every hospital had its own method for credentialing. At our institution, surgeons were credentialed based on their surgical practice, volume and past surgical history. Once they were credentialed they must be observed by an experienced pelvic floor surgeon for their first 5 cases. By no means is the certificate of attendance issued by Ethicon/Gynecare to be used for credentialing purposes. It was not meant for this purpose. Ever hospital has a credentialing committee which is responsible for the delineation of privileges.

Adequacy of Company IFU and Patient Brochures:

Ethicon/Gynecare had very detailed Instruction for Use (IFU) with all their sling products. They are very detailed and self-explanatory on all aspects of the procedures. We also made it a point to go over the IFU in detail during training sessions. They detailed the issues related to warnings and precautions associated with the procedures. All participants were given the IFU as well. The company also offered detailed brochures with resources available to the patients. These patient brochures were designed to provide information to a patient—not to take the place of the informed consent between that patient and her doctor.

The IFUs for Prolift are designed for pelvic floor surgeons—not patients. Based on my review of medical literature, my role as a professional education instructor, my interaction with hundreds of pelvic floor surgeons, my education and training, and my over thirty years of surgical practice, it is my opinion that the Prolift IFU and Ethicon's professional education materials such as the Prolift Surgeon's Resource Monograph adequately describe the risks that are specific or unique to Prolift. Moreover, the actual surgical risks and complications (as

opposed to warnings about alleged design deficiencies) that plaintiffs' experts opine should be included in the Prolift IFU are risks that are commonly known to pelvic floor surgeons. I base these opinions on the following:

The vast body of Prolift medical literature that extensively records success and complication rates associated with these devices. With many RCTs, prospective and retrospective cohorts multiple meta-analysis as documented above, no other POP product has had its safety profile so well documented as does this product.

Although I am not a regulatory expert, I have reviewed 21 C.F.R. 801.109(c), which provides for the omission of risk information if "the article is a device for which directions, hazards, warnings, and other information are commonly known to practitioners licensed by law to use the device." Additionally, the FDA's "Blue Book Memo" echoes this language, stating that information may not be included in a warning label if "the directions, hazards, warnings, and other information are commonly known to practitioners licensed by law to use the device…"

The FDA's 2008 and 2011 Public Health Notices which publically set forth the risks and complications associated with prolapse mesh devices like Prolift.

My education, training, and surgical experience, which include the implantation of over 500 transvaginal mesh procedures in addition to the patients I've treated who have had mesh implanted by other doctors.

My years of experience training other pelvic floor surgeons in treating POP with the Prolift system as well as other transvaginal mesh products. These training sessions not only allow me to instruct others, but provide me with a forum in which I have received a tremendous amount of feedback about the risks and complications associated with Prolift from other pelvic floor surgeons across the country.

My attendance at various medical conferences and professional society meetings, which include data about the performance of Prolift in the hands of a wide variety of pelvic floor surgeons. This data is often presented in the form of oral presentations, abstracts, and posters.

Biocompatibility of mesh:

The Prolene mesh that comprises Prolift is biocompatible with a well-documented history of safe and effective implantation in the pelvic floor. The allegation by many plaintiffs' experts that Prolene mesh is cytotoxic and harmful to pelvic floor tissue is without merit. Polypropylene mesh has been proven to produce a minimal inflammatory reaction in the body, especially when compared to other synthetic materials (Falconer, 2001). The 2015 Cochrane review notes that meshes like Ethicon's Prolene mesh have the "highest biocompatibility:"

> Type 1 mesh has the highest biocompatibility with the least propensity for infection. Differences in their efficacy and complications are likely to be due to several factors including the different knits and weaves of the various tape materials, their biomechanical properties and histological biocompatibility. Pore size affects the inflammatory response and resultant connective tissue formation within and into the mesh, and the rearrangement of materials such as collagen within the mesh structure. Macroporous meshes (pore size in excess of 75 μ m) easily allow macrophages, leukocytes, fibroblasts, blood vessels and collagen to transverse the pores: thus macroporous meshes promote tissue host ingrowth with resultant biocompatibility and low risk of infection (Amid 1997). Monofilament tapes are widely available and now predominate in current clinical practice.

Additionally, the 2014 AUGS/SUFU joint position statement notes the following:

- Polypropylene material has been used in most surgical specialties (including general surgery, cardiovascular surgery, transplant surgery, ophthalmology, otolaryngology, gynecology, and urology) for over five decades, in millions of

patients in the US and the world (personal communication with manufacturers of polypropylene suture and mesh). As an isolated thread, polypropylene is a widely used and durable suture material employed in a broad range of sizes and applications. As a knitted material, polypropylene mesh is the consensus graft material for augmenting hernia repairs in a number of areas in the human body and has significantly and favorably impacted the field of hernia surgery. As a knitted implant for the surgical treatment of SUI, macroporous, monofilament, light weight polypropylene has demonstrated long term durability, safety, and efficacy up to 17 years.

- The monofilament polypropylene mesh MUS is the most extensively studied antiincontinence procedure in history.
- Polypropylene mesh midurethral slings are the standard of care for the surgical treatment of SUI and represent a great advance in the treatment of this condition for our patients.
- This procedure is probably the most important advancement in the treatment of stress urinary incontinence in the last 50 years and has the full support of our organizations which are dedicated to improving the lives of women with urinary incontinence.
- Over 3 million MUS have been placed worldwide and a recent survey indicates that these procedures are used by > 99% of AUGS members.

I agree with the all these statements and other similar conclusions found in other professional society guidelines/statements. And while the above statement is directed towards slings treating SUI, it still bears on the mesh material in Prolift because they are both made of the same poloypropylene material. These statements are not only consistent with my own clinical experience treating thousands of women with polypropylene products, but these statements reflect the overwhelming consensus of the medical literature that I have read and reviewed during my career practicing medicine. The biocompatibility of polypropylene meshes like

Prolift's mesh is well established both in clinical practice (including my own) and the medical literature. Plaintiff's allegations are without merit and lack high level evidentiary support.

Malignant potential of mesh:

The malignant potential of implanted mesh in humans has been raised by plaintiffs. This can be attributed to animal studies done in 1958 by Dr. Oppenheimer. He demonstrated the development of sarcomas in rats implanted with sheets of plastic. However, more recent animal studies implanting monofilament and multifilament polypropylene mesh in mice, did not corroborate these findings. This phenomenon was related to the implanted materials physical traits with discs and sheets including pure metal, polymers, and glass being the most carcinogenic. These solid materials lose their carcinogenicity when they are implanted in porous or woven forms. An epidemiologic study by the International Agency for Cancer Research (IARC) in 2000 concluded that there is no evidence of tumorgenicity of metallic or synthetic implants in humans.

Surgeons at the Cleveland Clinic reviewed their mid-urethral synthetic slings performed between 2004 and 2013. During this period, 2,361 synthetic slings were performed and followed for 5-6 years. No sarcomas were found and their incidence of malignancy after mid-urethral sling was 0%. Their conclusion was there is no support for any association between polypropylene mesh used in mid-urethral slings and the development of malignancy in humans.

Surgeons at the Mayo Clinic reviewed their data from 2002-2012. During this period, 2,474 synthetic slings were placed. Median follow-up was 5 years. Their conclusion was that the development of pelvic malignancy after a mid-urethral synthetic sling is rare and unlikely to be secondary to foreign body reaction from implanted material.

The American Urogynecologic Society (AUGS) and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU), answered this question by stating 'Tumors related to the implantation of surgical grade polypropylene for mid-urethral slings in

humans have never been reported. There is no compelling evidence supporting human malignant transformation related to polypropylene despite millions of individuals implanted with various forms of this material spanning well over a half century world-wide.'

To date, there is no level I scientific data to conclude there is a correlation between the development of malignancy in humans with the implantation of polypropylene mesh products. They should be considered safe until scientific data proves otherwise.

A recent medline search on the malignant potential in humans implanted with polypropylene mesh, revealed no scientific data to support this claim.

Pore Size and Weight

Prolene Type I mesh is monofilament and manufactured with a pore size greater than 75 microns. Amid established that a macroporous mesh will have pores that are greater than 75 microns, and this is important for many reasons. Such construction promotes resistance to infection by allowing macrophages to enter the pores. Macrophages cannot enter pores that are less than 10 microns. Such design also allows greater type III collagen deposition, greater capillary penetration, and greater attachment strength. Gynemesh PS is large pore and light weight. It facilitates adequate tissue in-growth with minimal inflammation and foreign body reaction.

Knitted mesh has the highest porosity, lowest volume and largest interstices. Porosity allows the growth of fibroblasts around monofilaments without contraction bridges. This minimizes the foreign body reaction. The flexibility of the fiber in the lightweight macroporous graft facilitates a tension free repair and helps prevent stiffness in the vagina after augmentation.

The biology of prosthetic implant incorporation is accomplished in stages. By day 3 there is inflammation first exudative and then cellular. Polypropylene is the least inflammatory.

By day 10 there is fibroblast ingrowth and by week 6 complete ingrowth. The prosthetic strength doubles from week 3 to week 12.

The Prolift mesh is considered to be an Amid Type 1 mesh, and is commonly referred to as large-pore and lightweight mesh. Heavier meshes have greater and more prolonged inflammation. The hundreds of Prolift studies since ratify the fact that the mesh used to treat POP is highly biocompatible and yields low rates of complications and high rates of objective and subjective success. Prolene mesh also has greater scar plating and less elasticity once incorporated. Also, there is evidence of increased cell turnover ongoing inflammation and remodeling at one year. Furthermore, because tissues acting on the mesh can cause the mesh to shrink or contract, the fact that polypropylene meshes elicit a minimal foreign body reaction support my opinion that the mesh in Prolift does not contract or shrink in vivo in any clinically significant way.

Plaintiffs experts opine that a safer alternative design for the Prolift is Prolift +M because it's made of a lighterweight mesh--Ultrapro. In reality, the medical literature shows that the success and complication rates of Prolift and Prolift +M are clinically the same, as demonstrated by the three year follow-up of Prolift +M conducted by Milani (2012).

Degradation and Particle Loss

There is no clinical significance to claims of alleged particle loss and mesh degradation over time. AUGS and SUFU, which combined represent over 2,300 members, recently addressed the allegation that polypropylene mesh degrades. They concluded:

> Polypropylene is a stable and well-accepted biomaterial with a history of over five decades of use in mesh implants. In recent years, concerns regarding implanted polypropylene degradation have been raised as a result of very high magnification images that show portions of some explanted synthetic meshes with "cracked" surfaces. These surface changes were further hypothesized to lead to adverse clinical outcomes, though

this is not supported by the extensive peer-reviewed literature related to polypropylene mesh repairs. Prospective studies have followed patients with implanted mid-urethral slings for 17 years and show excellent durability and safety of the procedure.

I agree with this conclusion. Claims that mesh degrades and that particle loss is a matter of clinical significance is not supported by any level 1 evidence, nor have I experienced any complications attributable to alleged particle loss or degradation in my 20 years of clinical practice. A recent medline search on degradation and particle loss revealed no scientific data to support this theory.

In summary, the management of pelvic organ prolapse is a difficult and very challenging gynecologic condition. There is no one right answer for every patient. The treatment has to be tailored to the patients' needs and expectations. This is why options and preoperative evaluation and discussion is most important. The surgeon patient relationship must be based on trust, compassion, experience, knowledge, and honesty. Without this no surgical procedure should be deemed safe and effective.

The data, to date, overwhelmingly supports the use of Gynemesh PS and Prolift in the surgical management of POP. Every surgical procedure is fraught with risks, benefits, option, complications, side effects, and results. This occurs with native tissue repairs as well as transvaginal mesh repairs. It is up to the surgeon and the patient to decide what is best in their situation.

Based on my review of the literature, experience with my patients, discussion with colleagues and experts in the field, both nationally and internationally, It is my opinion that synthetic mesh augmentation in the management of pelvic organ prolapse is a safe and effective treatment in the appropriate selected patient.

I reserve the right to change my opinion if data contrary to the available data is presented.

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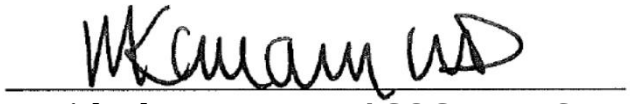

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